

EXHIBIT 4



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Assistant Secretary for Health
Office of Research Integrity
1101 Wootton Parkway, Suite 240
Rockville, MD, 20852

Phone 240-453-8800
FAX: 301-594-0043
Email: alexander.runko@hhs.gov
Web: <https://ori.dhhs.gov/>

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September 13, 2021

Tony M. Liss, Ph.D.
Provost and Senior Vice President for Academic Affairs
City College of New York
Wille Administration Building
3rd Floor
160 Convent Avenue
New York, NY 10031

TRANSMITTED VIA EMAIL TO: tliss@ccny.cuny.edu

RE: DIO 7470

Dear Dr. Liss:

The Division of Investigative Oversight (DIO), Office of Research Integrity (ORI), has received allegations of possible research misconduct from the National Institutes of Health (NIH) and anonymous complainants against Hoau-Yan Wang, Ph.D., Associate Medical Professor, City College of New York (CCNY).^{1,2} The allegations concern falsification and/or fabrication of data in research supported by U.S. Public Health Service (PHS) funds, specifically National Institute on Aging (NIA), NIH, grants P30 AG010124, P30 AG010161, R01 AG015819, RF1 AG059621, R01 AG040039, R44 AG050301, R01 AG057658, R21 AG056518, R01 AG055770, R01 AG054434, R01 AG067063, R44 AG057329, and R44 AG060878; National Institute of General Medical Sciences (NIGMS), NIH, grant R25 GM056833; National Institute of Mental Health (NIMH), NIH, grants P50 MH096891, R01 MH074672, R01 MH075916, R01 MH074313, R01 MH059852, and T32 MH014654; Office of the Director (OD), NIH, grant S10 OD010380; Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), NIH, grant U54 HD086984; National Institute of Neurological Disorders and Stroke (NINDS), NIH, grant R01 NS084965; and NIH contract 41545-00-02-05. The allegations stem from a recent submission of a “Citizen’s Petition” to the U.S. Food and Drug Administration (FDA) requesting that FDA halt ongoing clinical studies of

¹<https://www.ccny.cuny.edu/profiles/hoau-yan-wang>

²Dr. Wang is also a consultant for Cassava Sciences, Inc. (formerly Pain Therapeutics, Inc.).

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simulfilam in Alzheimer's Disease sponsored by Cassava Sciences due to concerns about the integrity of the data.³

The questioned research purportedly was conducted in Dr. Wang's laboratory at CCNY and was included in the following eight (8) PHS-supported published papers, one (1) PHS-supported poster, and one (1) grant application submitted for PHS funds:

- Banerjee A, Wang HY, Borgmann-Winter KE, MacDonald ML, Kaprielian H, Stucky A, Kvasic J, Egbujo C, Ray R, Talbot K, Hemby SE, Siegel SJ, Arnold SE, Sleiman P, Chang X, Hakonarson H, Gur RE, Hahn CG. Src kinase as a mediator of convergent molecular abnormalities leading to NMDAR hypoactivity in schizophrenia. *Mol Psychiatry* 2015; 20(9):1091-100 (hereafter referred to as "*Mol Psychiatry* 2015").⁴
- Talbot K, Wang HY, Kazi H, Han LY, Bakshi KP, Stucky A, Fuino RL, Kawaguchi KR, Samoyedny AJ, Wilson RS, Arvanitakis Z, Schneider JA, Wolf BA, Bennett DA, Trojanowski JQ, Arnold SE. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *J Clin Invest.* 2012 Apr;122(4):1316-38 (hereafter referred to as "*J Clin Invest.* 2012").⁵
- Wang HY, Capuano AW, Khan A, Pei Z, Lee KC, Bennett DA, Ahima RS, Arnold SE, Arvanitakis Z. Insulin and adipokine signaling and their cross-regulation in postmortem human brain. *Neurobiol Aging* 2019;84:119-130 (hereafter referred to as "*Neurobiol Aging* 2019").
- Wang HY, Lee KC, Pei Z, Khan A, Bakshi K, Burns LH. PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis. *Neurobiol Aging* 2017;55:99-114 (hereafter referred to as "*Neurobiol Aging* 2017").
- Meade GM, Charron LS, Kilburn LW, Pei Z, Wang HY, Robinson S. A model of negative emotional contagion between male-female rat dyads: Effects of voluntary exercise on stress-induced behavior and BDNF-TrkB signaling. *Physiol Behav.* 2021 May 15;234:113286 (hereafter referred to as "*Physiol Behav* 2021").
- Wang S, Li B, Solomon V, Fonteh A, Rapoport SI, Bennett DA, Arvanitakis Z, Chui HC, Miller C, Sullivan PM, Wang HY, Yassine HN. Calcium-dependent cytosolic phospholipase A2 activation is implicated in neuroinflammation and oxidative stress associated with ApoE4. *Mol Neurodegener.* 2021;16(1):26 (hereafter referred to as "*Mol Neurodegener.*" 2021).

³"Citizen's Petition" to FDA and supporting and related material: <https://www.regulations.gov/docket/FDA-2021-P-0930/document>

⁴DIO notes that while *Mol Psychiatry* 2015 is beyond the six-year time limitation specified in 42 C.F.R. § 93.105(a), Dr. Wang has cited this paper as recently as 2020, and the subsequent use exception (§ 93.105(b)(1)) applies to this paper.

⁵*J Clin Invest* 2012 would fall under the subsequent use exception (§ 93.105(b)(1)), as this paper was cited by Dr. Wang as recently as 2021.

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- Wang HY, Pei Z, Lee KC, Lopez-Brignoni E, Nikolov B, Crowley CA, Marsman MR, Barbier R, Friedmann N, Burns LH. PTI-125 Reduces Biomarkers of Alzheimer's Disease in Patients. *J Prev Alzheimers Dis.* 2020;7(4):256-264 (hereafter referred to as "*J Prev Alzheimers Dis.*" 2020).
- Stucky A, Bakshi KP, Friedman E, Wang HY. Prenatal Cocaine Exposure Upregulates BDNF-TrkB Signaling. *PLoS One* 2016 Aug 5;11(8):e0160585 (hereafter referred to as "*PLoS One* 2016").
- Wang HY, Pei Z, Xu Q, Brunelle L, Burns L, Thornton GB. SavaDx, a novel plasma biomarker to detect Alzheimer's disease, confirms mechanism of action of simufilam. Poster presented at: Alzheimer's Association International Conference (AAIC) July 31-August 4, 2021. San Diego, USA. (hereafter referred to as "AAIC Poster 2021").
- R01 AG073350-01, "Phase 2/3 clinical trial of sumifilam (PTI-125) in mild-to-moderate Alzheimer's disease," Lindsay Burns, Ph.D., Principal Investigator (P.I.), Hoau-Yan Wang, Ph.D., Co-Investigator, submitted to NIA, NIH, on October 3, 2020.

Specifically, Dr. Wang allegedly falsified and/or fabricated western blot data and plots of clinical trial data in:⁶

- Figures 4A, S2A, and S7 of *Mol Psychiatry* 2015
- Figures 4D and 4E of *J Clin Invest.* 2012
- Figure 5A of *Neurobiol Aging* 2019
- Figures 3 (right panel), 8B, 10A, and 12 of *Neurobiol Aging* 2017 (Figure 8B also appears as Figure 3B of R01 AG073350-01)
- Figures 8A, 8E, and 9A of *Physiol Behav.* 2021
- Figure 9A of *Mol Neurodegener.* 2021
- Figures 5B and 10A of *PLoS One* 2016
- Figure 3A of *J Prev Alzheimers Dis.* 2020
- Figures 4 and 5 of AAIC Poster 2021

⁶Some of the same allegations and additional allegations concerning non-PHS funded papers published by Dr. Wang were raised on the online platform for post-publication peer review, PubPeer: <https://pubpeer.com/search?q=Hoau-Yan+Wang>

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Since the questioned data were supported by PHS funds, ORI has jurisdiction in this matter. There is no presumption of wrongdoing. However, the allegations are of serious concern and require a prompt and thorough assessment to determine whether further action is necessary. Therefore, ORI requests that CCNY conduct an inquiry, in accordance with § 93.307.

In an attempt to help you and the inquiry committee review the issues in a way that will be fully compliant with ORI's requirements for oversight review, DIO has listed some of the specific issues relevant to the PHS interest in this case. Specifically:

1. As required by § 93.307(a), institutions must sequester evidence either **before** or when the institution notifies the respondents of the allegation, inquiry, or investigation. ORI emphasizes that this timing of the sequestration process prior to notification of the respondents is critical for ensuring the integrity of the research record and other relevant evidence.

As required by § 93.307(b) and § 93.310(d), CCNY must take all reasonable and practical steps to obtain custody of all of the research records and evidence needed to conduct the research misconduct proceeding during the inquiry, inventory the records and evidence and sequester them in a secure manner. If additional items become known or relevant to the inquiry or subsequent investigation, please take appropriate steps to properly sequester and obtain the evidence. Instructions for Submitting Files and Evidence to ORI are enclosed with this letter for your convenience. Please note that ORI has issued a notice regarding the sequestration of evidence during office/building closures due to the COVID-19 pandemic.⁷

2. CCNY should pursue diligently all significant issues and leads discovered that are determined relevant to the inquiry or subsequent investigation (per § 93.310(h)), including any evidence of additional instances of possible research misconduct, such as in other papers published by Dr. Wang or manuscripts submitted but not accepted for publication, submitted or awarded PHS grant applications, progress reports, posters, presentations, and other research records, subjects to the time limitations stated in § 93.105. Recently, ORI has issued a notice of information about the scope of research misconduct in institutional proceedings⁸ and provided several hypothetical case examples for reference.⁹

Additional concerns were raised in the "Citizen's Petition" and by NIH¹⁰ in other PHS-funded and non-PHS funded papers published by Dr. Wang. However, CCNY will need to examine the original data records to determine if the figure image artifacts or anomalies identified could constitute potential falsification and/or fabrication.

⁷<https://ori.hhs.gov/blog/ori-guidance-institutions-concerning-sequestration-during-closure-institutions-due-covid-19>

⁸<https://ori.hhs.gov/blog/notice-information-about-scope-research-misconduct-institutional-proceedings>

⁹<https://ori.hhs.gov/sites/default/files/2021-05/Scope%20of%20Research%20Misconduct%2005-27-2021.pdf>

¹⁰Pages 19-62 in the enclosed "NIH Image Analysis - DIO 7470.pdf"

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3. The allegations should be re-framed to ensure that there is sufficient information to identify the issues that concern PHS under its definition of research misconduct and CCNY's analysis conducted during the inquiry and/or subsequent investigation to support a finding a research misconduct. The re-framed allegations should address who (one specific respondent), did what (falsified/fabricated/plagiarized), where (publications, grant applications, research records), and specifically how (duplicated, cut and pasted, deleted, altered, etc.). For example:
 - Allegation 1: Respondent (falsified/fabricated/plagiarized) Figure (#) in (publication/grant application/document) by doing "X."

"X" should describe the specific falsification/fabrication, such as "by using the same data panel in Figure # of publication X, when the figure represented results from different experiments." If the false figure was used in another figure, state the figure number and the publication or grant application number involved.
4. The prospect of more than one researcher being responsible for the alleged falsification and/or fabrication should be considered. Notably, laboratory members and coauthors who were involved in generating the primary data or creating the figures in the published papers, poster, and grant application should be considered as respondents in the inquiry. If any additional respondent(s) are identified throughout the research misconduct proceedings, including an investigation, they are to be notified of the allegations, in accordance with § 93.307(b), §93.308(a), and § 93.310(c).
5. In accordance with § 93.104, requirements for a research misconduct finding require that:
 - a) There be a significant departure from accepted practices of the relevant research community; and
 - b) The misconduct be committed intentionally, knowingly, or recklessly; and
 - c) The allegation be proven by a preponderance of the evidence.

At the conclusion of its investigation, CCNY must determine if a respondent's actions while reporting the data in the published papers, poster, and grant application constitute acts of intentional, knowing, or reckless falsification and/or fabrication, as defined in § 93.103, and/or if the questioned images were the consequence of honest error, miscommunication, poor record keeping, or questionable or unacceptable research practices.

An inquiry into possible research misconduct should be initiated promptly upon receipt of an allegation of possible research misconduct and should be completed within the 60 days specified in the PHS regulations. Therefore, we would expect to receive your report on or about November 9, 2021. Please note that recently ORI has issued a notice regarding delays in research misconduct proceedings due to the COVID-19 pandemic.¹¹ An institution may submit a written request via

¹¹<https://ori.hhs.gov/blog/ori-operations-status-during-public-health-emergency-united-states-2019-novel-coronavirus>

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email to Michael.Peters1@hhs.gov if an extension is needed for completion of its inquiry. Please provide an explanation of the circumstances or reasons that warrant a longer period for completion of the inquiry, in accordance with § 93.307(g). In addition, ORI has issued an update for institutions on the submissions of files and documents to ORI.¹²

Enclosed for your convenience are an Inquiry Report Checklist for documents that should be provided with inquiry report and an Outline for an Inquiry Report as well as the previously referenced Submitting Files and Evidence to ORI, AAIC Poster 2021, NIH's image analysis, and the NIH grant application. Please note that grant applications are not part of ORI's system of records (SOR) but rather belong to NIH's SOR and may not be shared with anyone without a strict need to know.

Finally, ORI's mission in protecting PHS funds complements that of NIH. Both NIH and recipient institutions are stewards of those funds, as explained in the NIH Grants Policy Statement (<https://grants.nih.gov/policy/index.htm>). Consistent with § 93.401, ORI works closely with NIH to share relevant information related to research misconduct proceedings. To ensure that NIH has the information it needs to work with the applicant/grantee institution to protect the funds and research, CCNY also should communicate directly with NIH, if necessary. Specifically, if the allegations in this matter rise to a level that involves the health and safety of the public, including human or animal research subjects, the misuse of NIH grant or contract funds, foreign influence, or if there are other considerations under § 93.309(d), CCNY should directly contact Dr. Patricia Valdez, NIH Extramural Research Integrity Officer, at patricia.valdez@nih.gov or at 301-451-2160. To protect the confidentiality of the matter(s) between NIH and your institution, please do not contact any other NIH program officials or scientific review officers and solely communicate with Dr. Valdez.

If you have any questions regarding the handling of this case, or questions about technical matters, please contact me at 240-453-8800 or via email at alexander.runko@hhs.gov.

Sincerely,

Alexander P. Runko

Digitally signed by Alexander P. Runko -S

-S

Date: 2021.09.13 11:28:20 -04'00'

Alexander Runko, Ph.D.

Director

Division of Investigative Oversight

Office of Research Integrity

Enclosures

¹²<https://ori.hhs.gov/blog/update-ori-file-submission-process>